Title: The association of Val109Asp polymorphic marker of intelectin 1 gene with abdominal obesity in Kyrgyz population

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Author’s response to reviews:

RE: Manuscript BEND-D-17-00156
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To the Editor:

We appreciate very thorough and conceptual evaluation of our manuscript, as we thank the Editor and the Reviewer for addressing most problematic statements in the manuscript. In the following detailed response, we address each critique calling for changes point-by-point, indicating where relevant additional text has been added to the body of the manuscript and its location.

Reviewer 1:

This study examined the association of a SNP in the omentin gene with abdominal obesity in a Kyrgyz population. The authors report that the SNP, Val109Asp (rs2274907) is associated with abdominal obesity, with homozygotes for the Val allele having an increased risk (OR=3.12). The overall concept is fine, but I have concerns with the dated approach that was used, the small sample size, and the over-interpretation of the results.
We appreciate this most important point in this manuscript. We fully agree that small sample size is a true limitation of this study, and we have probably used strong statement in the interpretation. Since each of these critiques are discussed in detail below, we address each of them separately.

1) Technically, the method used for SNP genotyping (RFLP) is accurate, and my primary concern is that only one SNP was examined. Abdominal obesity is clearly a multifactorial trait, and in an era of GWAS, next-generation sequencing, and "omics" based analyses, it seems dated to draw much inference from the results of a single SNP.

Indeed, we agree that in the era of GWAS, SNP studies may look outdated. There are, however, a number of reasons behind the novelty of this study for Central Asia, which we have decided to narrate on in the following paragraph, now included in the Discussion: “We need to state that currently full-genome studies in Kyrgyz Republic are not feasible. Studies on multifactorial diseases in our country are still limited with single nucleotide polymorphism search only. The current study is the first and only to assess Val109Asp polymorphism of ITLN1 gene in the whole Central Asian population, and also one of very few uncovering the association of ITLN1 gene with AO. This study enabled to test the distribution of genotypes and alleles of ITLN1 gene’s Val109Asp polymorphism in Kyrgyz population, as well as to detect significant increase in Val109Val genotype frequency in patients with AO. This may support the hypothesis of the role of ITLN1 in genetic predisposition to AO in the Kyrgyz. Such conclusion clearly needs further confirmation in larger samples and with other genetic markers.”

2) The small sample size also limits enthusiasm for this study. While the results may be statistically significant (although only marginally, p=0.043), this is essentially based on 15 cases and 7 controls who were homozygous for the Val allele. If only one of the control individuals were to change from a heterozygote to a homozygote, or vice versa for the cases, the results would no longer be significant (p=0.07).

We certainly agree with this narration and the assumption on the shift to non-significant outcome if only one control changes to homozygous. Because this point should be interpreted with the following comments #3, we address them together below.

3) The interpretation is that this particular SNP is associated with abdominal obesity in this population. This is technically correct based on the statistics (although point 2 above should be considered), but the association is extremely modest, even though the effect size appears large. This could be presented as borderline support of data from previous studies, but the
authors appear to put too much emphasis on the result. The authors state that the SNP "...should be considered as an established prognostic marker of developing AO." This is an extreme over-statement for a very modest single SNP association with a complex trait.

We appreciate this comment and have to admit that our statements were way too strong in the previous version of the manuscript. To correct that, we have amended the conclusions section in the abstract to read: “Significant increase in the frequency of Val109Val genotype of ITLN1 gene in AO patients may be indicative of some potential role of ITLN1 gene in molding genetic predisposition to AO in the Kyrgyz. This requires further elaboration in the future studies.” We also elected to remove the sentence “Therefore, homozygous genotype of Val109Val polymorphic marker of ITLN1 gene should be considered as an established prognostic marker of developing AO” from the manuscript. Similarly, we removed the sentence “In testing the association of genotypes with AO, we found that the homozygous genotype of the less spread Val109Val allele was a marker in increased likelihood of AO in Kyrgyz population (OR=3.12; 95% CI 1.23–7.90). In contrast, we failed to identify statistically significant association of Val109Asp polymorphic locus allele with AO”.

In Conclusions, we also removed the sentence “We have identified positive association of Val109Val homozygous genotype with abdominal obesity in Kyrgyz population.” and replaced it with “Significant increase in the frequency of Val109Val genotype of ITLN1 gene in AO patients may be indicative of some potential role of ITLN1 gene in molding genetic predisposition to AO in the Kyrgyz”. We also considered it germane to put an additional sentence in the very first paragraph on Discussion to read: “In the given population, significant increase in the frequency of Val109Val genotype of ITLN1 gene in AO patients may be indicative of the association of ITLN1 gene with AO, which requires further investigation”.

Other minor concerns:
The official gene name (intelectin 1) and symbol (ITLN1) should be used instead of "omentin."
Done. We are now using the official gene name (intelectin 1) and its abbreviation (ITLN1).
The two alleles should be referred to as "major" and "minor" throughout.
In the revised version, we refer to either major or minor alleles, whenever possible.
Once again, thank you for these detailed reviews. We believe that the manuscript is substantively improved with these changes.
Sincerely,
Dr Jainagul Isakova, Corresponding Author